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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/605,708	GONG ET AL.	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,9-15,20,21,24,30-32 and 35-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 9-15, 20-21, 24, 30-32, 35-44 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed October 7, 2008 have been received and entered. Claims 1-3, 9-15, 20-21, 24, 30-32 and 35-45 are pending in this application.

Election/Restrictions

Applicant's election of claims 1-16, 20-21, 29-32 and 35-41 in the reply filed on January 19, 2006 was acknowledged. The applicants elected muscle specific promoter examination. It was noted claim 19 included muscle specific promoter and therefore claim 19 was rejoined with elected groups. Additionally, claim 24 was also rejoined for the examination purposes to the extent it read on elected invention.

Claims 1-3, 9-15, 20-21, 24, 30-32, 35-44 and 45 are currently under examination.

Oath/Declaration

The Gong declaration filed on October 7, 2008 under 37 CFR 1.132 is not sufficient to overcome the rejection of claims 1-3, 9-15, 20-21, 24, 30-32, 35-44 and 45 under 35 U.S.C. 112 First paragraph. The declaration will be discussed in detail below as it applies to the rejection.

Maintained-Claim Rejections-35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 9-15, 20-21, 24, 30-32, 35-44 and 45 remain rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for

(1) a method of providing transgenic fish to the ornamental fish market comprising the step of

(a) obtaining a stable germline transgenic ornamental fish comprising a chimeric gene comprising a promoter that drives the expression of a fluorescent protein selected from a group consisting of BFP, YFP, CFP and GFP in muscle cells of said fish, said promoter being zebrafish fast skeletal muscle isoform of myosin light chain 2 gene promoter,

wherein said transgenic fish expresses fluorescent protein encoded by fluorescent gene in skeletal muscle at a level sufficient such that said transgenic fish exhibit visible fluorescence upon exposure to sunlight , and

(b) distributing said fish to the ornamental fish market.

does not reasonably provide enablement for using any other muscle specific promoter to obtain stable transgenic fish line suitable for ornamental fish market showing fluorescence upon exposure to sunlight or any transgenic fish showing more than one fluorescent protein in the same tissue to effect a new fluorescent color that is visible after exposure to sunlight or mating fish across genera or family.

Applicants' arguments filed October 7, 2008 have been fully considered but are not persuasive.

"Use of any muscle specific promoter"

Applicants argue that instant specification teaches that one can screen the transgenic fish embryos to select those embryos exhibiting the desired expression characteristics. Particularly, preferred are those embryos exhibiting high expression such that the fluorescence is visible in the sunlight Applicants direct to figure 8-12 for the assert that example 3 and figure 12 provide adequate guidance to screen transgenic embryo (Gong Declaration, para. 5). Applicants also cite the declaration of Gong and assert that the muscle occupies a large part of the fish body and thus has the capacity to synthesize enough proteins for visible fluorescence, screening for

visible fluorescence using any muscle-specific promoter provides specific guidance and predictable results for obtaining stable transgenic fish suitable for the ornamental fish market (Gong Declaration, para. 6, argument page 3). Applicants assert based on successful working examples of muscle specific promoters that may be used in the claimed method, the present specification enables those of ordinary skill in the art to practice the claimed method. Applicants also cite the post filing reference of Kinoshita (Fisheries Science, 2004, 70, 645-649) and Chou et al (Transgenic Res., 2001, 10, 303-315) for the enabling support.

In response, it is noted that contrary to applicants' argument the claimed method uses a muscle specific promoter that shows strong fluorescence in presence of sunlight to generated transgenic fish line. In the instant case, the issue is not whether one of skill in the art would be able to test different muscle specific promoter to show fluorescence under sunlight. Instead the issue is whether at the time of filing of this application, instant specification provided adequate guidance with respect to use of any muscle specific promoter derived from any species in generating transgenic fish that would show strong fluorescence under normal sunlight without undue experimentation and with a reasonable expectation of success (emphasis added).

In fact, prior to instant invention, as stated in previous office action transgenic fish that are capable of expressing heterologous gene under the control of different promoter including muscle specific promoter were generally known in prior art (see Moss et al, Higashijima et al, Kuo et al, Kim et al, Hackett et al, all art of record). However, in spite of extensive teaching in the prior art showing multiple constructs being reproducibly expressed in tissue specific manner, none of the promoters were suitable for use in generating transgenic ornamental fish because an unusually high level of expression is required in the muscle tissue to be of ornamental value. It was also noted that applicants have previously argued and provided evidence indicating that transgenic zebrafish line generated by

Higashijima et al (Dev Biol. 1997; 192(2): 289-99, IDS) and cited by Examiner that comprises a fluorescent gene under the control of beta actin promoter (page 295, col. 1, para 2, Fig 4) could not be viewed in sunlight because of weak fluorescence (see the email of Dr. Hitoshi Okamoto and applicants" argument page 9, para. 1-3, dated 2/20/2008). In fact, Dr. Okamoto confirmed in an email exchange with Dr. Gong that the GFP and RFP transgenic zebrafish lines under the mylz2 promoter disclosed by Gong et al displayed strong visible fluorescent colors in adult fish even under the normal daylight that was not observed in the actin promoter fish described in the Higashijima article in sunlight (emphasis added by applicants see page 9 para. 2 and email) suggesting the novelty of this invention is the unusually high level of activity of the promoter and it is not predictable that any other promoter, including muscle-specific promoters, would have this activity level without undue experimentation (emphasis ours).

Applicants' arguments and Gongs' declaration citing the references of Chou et al and Kinoshita et al that those of skill in the art were aware that certain design or screen choices may need to be made in order to achieve an optimally performing transgenic fish with muscle specific promoters is not persuasive. It is noted that Chou et al (Transgenic Res., 2001, 10, 303-315) in a post filing art report for the first time the importance and feasibility of using AAV-ITR for more efficient and tissue specific expression of beta actin promoter. It is noted that Chou et al for the first time suggested that AAV-ITR not only enhances the tissue, specificity, but also enhances the expression of exogenously introduced gene under the control of specific promoter (see page 312, col. 1, para. 2). It is also disclosed that, irrespective of promoter type, none of the transgenic embryos injected with non-ITR containing DNA fragment showed uniform GFP expression at F0)see page 312, col. 2, para. 1). In fact, Chou et al states' [t]o our knowledge this is the first report of a transgenic GFP reporter gene being uniformly and strongly expressed in the F0 generation (see figure 6C, page 312, col. 2, last line). MPEP 2164.05(a) [R-2] states "[T]he state of

the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1325-26 (Fed. Cir. 2004) ("a patent document cannot enable technology that arises after the date of application"). Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. *In re Gunn*, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA 1976); *In re Budnick*, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976). In the instant case, applicants are relying on the inventive embodiment of post filing disclosure of Chou et al to support the enabling disclosure of the instant application. It is noted that neither specification nor prior art contemplated using AAV-ITR to flank GFP cDNA under the control of any muscle specific promoter to produce transgenic fish. Similarly, applicants' argument and reliance on the teaching of Kinoshita M (Fisheries Science, 2004, 70, 645-649) for the enabling support of instant specification, it is emphasized that medaka skeletal muscle actin promoter disclosed by Kinoshita to produce transgenic medaka was not characterized prior to filing of application from which instant application claims priority. It is noted that Kinoshita cite reference (see ref. 14 of Fisheries Science, 2004, 70, 645-649) that characterize medaka skeletal muscle actin promoter to show that the muscle-specific expression of both OlMA1 and OlMA2 is regulated by relatively short regions directly upstream from +1. As for skeletal actin OlMA1, a sequence beginning only 949bp upstream from +1 is sufficient for strong expression in skeletal muscle. The most upstream end of this region, from -949 to -662, which we named MA1e, seems to act as a skeletal muscle specific enhancer, and it cooperates with the region between -421 and -201, which we named the P1 region. Constructs with deleted MA1e gave significantly reduced muscle-specific signal, even if they contain P1 region. Thus, in view of foregoing it is apparent that Kinoshita M (Fisheries Science, 2004, 70, 645-649) required extensive guidance of skeletal

muscle specific regulatory sequence capable of directing expression of GFP in fish that was not routine and would require undue experimentation without reasonable expectation of success. These assertions are supported by the applicants' own post filing art that states "availability of several GFP transgenic zebrafish that have been produced using many different tissue-specific including muscle specific promoters (also see references therein), but none of these transgenic lines display fluorescent color visible to unaided eyes. Thus, one key to success in the generation of colorful transgenic ornamental fish is in the strength of the promoter. Another factor is the selection of tissue; the muscle constitutes majority of the body and thus synthesizes more and visible color proteins. In contrast, transgenic GFP expression in only a single layer of skin cells cannot be visualized without using a fluorescent microscope (Gong et al, Biochem Biophys Res Commun. 2003; 308(1): 58-63, supra, page 62, col. 2, para. 1 art of record)". Although, instant application recognizes expression of GFP transgene in muscle but fails to provide adequate guidance with respect to use of muscle specific promoter capable of displaying fluorescent color visible to unaided eyes under sunlight commensurate with full scope. An artisan would have to perform undue experimentation to make use of the invention without reasonable expectation of success.

Applicants also argue that nowhere Gong et al imply that MLC2 promoter is vital to produce fluorescent transgenic fish. Applicants cite the review article of Hackett *et al.,* "The Molecular Genetics of Transgenic Fish" that is published in 2000 to show that an abundance of tissue specific and other promoters that were all routinely found to be operable in fish. See, for example, Tables 1 through 3 (see page 5, last para. of the argument).

As an initial matter, the statements of Examiner that are cited by applicants are not the quotes of Gong. Examiner would agree with applicants' assertion that Gong et al nowhere imply that MLC2 promoter is vital to produce fluorescent transgenic fish. However, the issue is not whether MLC2 promoter is vital to

produce fluorescent fish for ornamental fish market. As stated in the previous office action, based on applicant's disclosure, it appears that the intended purpose of obtaining transgenic fish is to provide fluorescent fish to ornamental fish market for display purposes. Furthermore, it is generally known in the art and described by applicants that ornamental and aquarium fish are defined as fish that are produced and maintained solely for exhibit purpose (see applicants' argument and FDA fish classification Guide, filed 8/11/2006, page 13, art of record). Thus, the sole purpose of generating transgenic fish is to produce fish that are capable of displaying fluorescent color visible to unaided eyes under sunlight. Gong et al (Biochem Biophys Res Commun. 2003; 308(1): 58-63, art of record) summarized the state of art in generating transgenic fish suitable for ornamental fish market and report the '[a]vailability of several GFP transgenic zebrafish that have been produced using many different tissue-specific including muscle specific promoters (also see references therein), but none of these transgenic lines display fluorescent color visible to unaided eyes. Thus, one key to success in the generation of colorful transgenic ornamental fish is in the strength of the promoter. (Gong et al, supra, page 62, col. 2, para. 1)". It is noted that applicants in post filing art have described in spite of availability of several transgenic line that uses tissue specific promoters, none of these transgenic fish made by using tissue specific promoter were suitable for ornamental fish market. Gong et al clearly suggest importance of strength of the promoter in obtaining transgenic fish suitable for ornamental fish market (emphasis added).

Gong et al (Biochem Biophys Res Commun. 2003; 308(1): 58-63, art of record) in post filing art report fluorescent proteins that are expressed under a strong muscle-specific *mylz2* promoter in stable lines of transgenic zebrafish display vivid fluorescent colors (green, red, yellow, or orange) visible to unaided eyes under both daylight (abstract).

It is in this context, Examiner stated that it is apparent that choice of a promoter could greatly effect the level of expression in transgenic ornamental fish. It is clear from the teaching of Gong et al that strong expression of fluorescent gene under the control of muscle specific promoter such as one exemplified by Gong and disclosed in the instant application would be required for successfully generating transgenic fish for distribution in ornamental fish market.

In response to the reference of Hackett *et al*, it is emphasized that the issue is not whether muscle or tissue specific promoters operable in fish were known in prior art, rather the issue is whether prior art provided guidance with respect to muscle specific promoter that were strong enough to display fluorescent color in fish that was visible to unaided eyes under sunlight. In fact, as stated in preceding section post filing art of Gong et al recognized lack of such guidance in prior art three years after the publication of Hackett *et al*, and report the '[a]vailability of several GFP transgenic zebrafish that have been produced using many different tissue-specific including muscle specific promoters (also see references therein), but none of these transgenic lines display fluorescent color visible to unaided eyes.

In the instant case, claims are drawn to obtain a transgenic fish comprising chimeric genes under control of any muscle specific promoter that drives the expression of a fluorescent protein and distributing such fish in ornamental fish market. It is apparent from the teaching of Gong et al that generation of transgenic fish that is suitable for distribution in ornamental fish market requires strong muscle specific promoter, which may require exposure of fish to a light of specific wavelength selected to be optimal for the fluorescent protein in order to visualize fluorescence on the fish. In view of foregoing discussion it is apparent that specification has failed to provide relevant teachings or specific guidance correlating to transgenic fish comprising fluorescent gene under control of any muscle specific promoter other then exemplified muscle specific promoters that are suitable for generating transgenic ornamental fish intended for distribution in ornamental fish

market showing contemplated biological activity. In fact, the prior art , specification and post filing art reports that not all muscle specific promoters function would function in same manner as descibed in the specification and it would be unpredictable which fragment of other tissue specific promoter would show higher level of expression in muscle tissue that constitutes majority of the fish body tissue is key to success in generating transgenic fish for ornamental fish market (supra). It is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). In the instant case, the specification has failed to report obtaining a transgenic fish line comprising a gene encoding a fluorescent protein under the control of any other muscle specific promoter except specifically those exemplified in the instant specification being suitable for distribution to ornamental fish market. An artisan would have to perform undue experimentation to make and use the invention commensurate with the full scope without reasonable expectation of success.

"More than one fluorescent protein in the same tissue"

Applicants argue that specification provides guidance as to how to provide transgenic fish with more than one fluorescent proteins in the same tissue, for example, in paragraph [0092] (see argument page 6).

In response, it is noted that paragraph [92] of the specification describes multiple color fluorescent fish may be generated by the same technique as blue fluorescent protein (BFP) gene, yellow fluorescent protein (YFP) gene and cyan fluorescent protein (CFP). The specification contemplates by expression of two or more different fluorescent proteins in the same tissue, an intermediate color may be

created. In the instant case, claims are directed to creating transgenic ornamental fish that show more than one fluorescent protein in the same tissue upon exposure to sunlight. It is generally known in the art that sunlight is uniform in color and is actually composed of a broad range of radiation wavelengths in the ultraviolet (UV), visible and infrared (IR) portions of the spectrum. Red light consists of light waves with a wavelength of about 700 nanometers (billionths of a meter), yellow light has wavelengths of about 550 nanometers, and blue light has wavelengths of about 450 nanometers. But the wavelengths of colored light are not limited to specific ranges. Thus, claims require expression of plurality of different fluorescent protein in same tissue suggesting intermediate colors of unknown excitation/emission spectra. For instance, waves that have wavelengths of 600, 625, 650, and 675 nanometers would have orange, orangish-red, reddish-orange, and, finally, red colors or other intermediate color combination. These different yet to be discovered color combination may overlap or shift the excitation/emission spectra in sunlight. The guidance provided in the specification is limited to generating transgenic fish expressing GFP (see example 4). The specification and art of record fails to support any other intermediate fluorescent protein or combination of fluorescent protein other than GFP, where emission is visible to the unaided eye. Absent of evidence to the contrary, it is not clear that yet to be discovered color combination that may overlap or shift the excitation/emission spectra in sunlight would be functional in the same manner as they have been demonstrated for the exemplified GFP-transgenic zebrafish. An artisan would have to perform undue experimentation to make and use the invention without reasonable expectation of success.

"Mating fish between different genera and families"

Applicants argue that Examiner supports the position of enablement of this claimed subject matter comprised in dependent claim. Applicants assert that Bartley et al. fully evidences the broad knowledge in the art for making inter-specific

hybrids. Therefore, careful design in routine practice could avoid problems disclosed in Bartley.

In response, contrary to applicants' argument, although inter-specific hybrids were known in prior art, the claimed subject matter is not limited to generating only fish but to generate a transgenic line. In the instant case, inter-specific hybrids are not predictable because claims embrace mating transgenic fish of one species to fish of another species of different and divergent genera and families to obtain the transgenic line comprising one or more chimeric gene under the control of any muscle specific promoter and exhibit fluorescence under normal sunlight(emphasis added). It is noted that recitation of use of different species encompasses mating fish of different orders, family and genera.

The art at the time of filing held that while interspecies crossing within a genus can often occur and can also be desired (also evidenced by Bartley), however, crossing of distantly related species of the same genus as well as crossings of fish between different genera and families are highly unpredictable as to the success of the fertilization, development, health of any progeny that do occur and fertility of offspring. The specification teaches making transgenic fish expressing a transgene encoding a fluorescent protein by microinjection of DNA into the cytoplasm of 1- or 2-cell stage embryos a 1-celled embryo using fish species that lay eggs that are fertilized and develop outside of the mother. The specification teaches operably linking the fluorescent protein-encoding genes to muscle specific MLC2f promoter or MCK promoters that result in expression of the fluorescent protein. The specification teaches crossing the transgenic zebrafish fish to fish of the same wild type species showing similar level of fluorescent expression (See example 3). The guidance provided in the specification is limited to the specification teaching use of closely related Danio (zebrafish) species of fish.

The specification failed to disclose extrapolating the same teaching to live bearing fish either in transgenesis or in crossing to obtain the transgenic offspring.

The reference of Bartley et al (Reviews in Fish Biology and Fisheries 2001,10: 325–337) is applied to the extent to show that inter specific hybrids even within the same genera could be variable and depend on the genetic structure of the parent fish. Bartley et al teaches that inadvertent hybridization and backcrossing can lead to unexpected and undesirable results in hybrid progeny, such as failure to produce sterile fish, loss of color pattern, and reduced viability (see abstract). Bartley et al also discuss hybridization between species often results in offspring that are sterile or with diminished reproductive capacity as a result of problems in gonad development and chromosome pairing (page 330 col. 1, last para, bridging to col. 2). The specification fails to set forth, of the many families of fish, which species of fish would provide valuable hybrid offspring (emphasis added). It was indicated that the specification fails to support that transgenic zebrafish could crossed with any other fish encompassed by the claims such as guppy, Molly or pangasius. Furthermore, it would be unpredictable how strong MLC2f promoters would be in hybrid species, particularly since art teaches importance of strength of the promoter in obtaining transgenic fish suitable for ornamental fish market. Absent of evidence to the contrary, it is not clear that MLC2f promoter would be functional in hybrid species in the same manner as they have been demonstrated for parent species. The lack of guidance in the specification would force the skilled practitioner to guess and try crossing different species of wild type fish to make transgenic ornamental fish showing no loss of fluorescent color when exposed to ultraviolet or sunlight. Such guessing would require extensive and undue experimentation. Applicant should note that "case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970.

In conclusion, in view of breadth of the claims and absence of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by applicant is not enabled for the claimed inventions

commensurate with full scope of the claim. The specification and prior art do not teach method of obtaining transgenic fish of any species comprising fluorescent gene under control of any muscle specific promoter and distributing said fish to ornamental fish market commensurate with full scope of the claims. An artisan of skill would have to perform undue experimentation to make and use the invention because the art of making transgenic fish using any promoter for distribution of said fish in ornamental fish was unpredictable at the time of filing of this application as supported by the observations in the art record.

Maintained-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 9-15, 20-21, 24, 30-32, 35-44 and 45 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants' arguments filed October 7, 2008 have been fully considered but are not persuasive. Applicants' argument is based on (i) the fact that muscle specific promoters were well known as of the filing date is evidenced by evidence set forth above in the enablement section of this response and (ii) many different species of fish have now been genetically engineered such that now the genetic engineering of fish is generally routine (page 7 , last para. of the argument and page 8, para. 1).

As an initial matter instant written description rejection is not based on enablement issues pertaining to genetically modifying fish or generating transgenic

fish using any muscle specific promoter as argued by the applicants. Examiner would agree that one of skill in art would be able to make transgenic fish using any promoter. The issue is whether applicants' have described with distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed genus of muscle specific promoter that would display fluorescence in a transgenic fish under normal sunlight. The analysis is based on whether specification teaches essential or critical elements or which are not adequately described in the specification and which are not conventional in the art as of the applicants' effective filing date for genus of muscle specific promoter derived from any species that would be strong enough to display fluorescence under normal sunlight.

In the instant case, claims are directed to a transgenic fish line comprising a chimeric gene that is positioned under the control of any muscle specific promoter such that said fish expresses fluorescent protein encoded by the gene in the skeletal muscle upon exposure to sunlight or ultraviolet light. The claims encompass a large number of muscle specific promoters that show contemplated biological activity of displaying fluorescence under normal sunlight in plurality of different fish. The claims thus constitute a claimed genus that encompasses muscle specific promoter of any species that would show desired expression of fluorescent gene under normal sunlight, yet to be discovered.

In analyzing whether the written description requirement is met for the genus claim, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics, specific features and functional attributes that would distinguish different members of the claimed genus. The claims embrace transgenic fish line of any species that comprises a chimeric gene under the control of any muscle specific promoter showing expression of fluorescent protein upon exposure of any light including sunlight.

The specification teaches only two constructs (2011 bp and 1338 bp) that are capable of maintaining the high level of expression, while the highest expression was obtained only with the 2-kb promoter, indicating the importance of the promoter region of 1338 bp to 2011 bp for conferring the highest promoter activity required for strong fluorescence expression upon exposure to sunlight (see para 89 and 90 of the published application) (emphasis added). Additionally, specification teaches only one species of transgenic fish line (zebra fish) comprising chimeric gene under the control of one species of muscle specific promoter (MLC2f promoter), wherein the transgenic founder zebrafish containing pMLC2f-EGFP emit a strong green fluorescent light under a blue or ultraviolet light and the transgenic offspring obtained after the crossing transgenic founders with wild-type fish displayed strong green fluorescence that was found high enough to show green fluorescence when the fish are exposed to sunlight.

It is emphasized that the specification is silent, however, on any other muscle specific promoter or any other variant of MLC2f that would show contemplated biological function of showing strong expression upon exposure to sunlight. The specification additionally fails to disclose the nature of the association of genus of other muscle specific promoter that would show fluoresce upon exposure to any light. The claims thus constitute a genus that encompasses plurality of different muscle specific promoter or their fragments yet to be discovered, and since the specification only discloses a single species of MLC2f promoter that may be capable of showing fluorescence upon exposure to any light including sunlight, the disclosed structural features of said MLC2f do not constitute a substantial portion of the claimed genus.

As such, the Artisan of skill could not conclude that Applicant possessed any additional species, except for that of a zebra fish comprising a chimeric gene under the control of a fast skeletal muscle isoform of myosin light chain 2 gene promoter which includes the sequence of SEQ ID NO:22. Hence, only the transgenic

ornamental fish comprising chimeric gene under control of MLC2f promoter could be demonstrated as possessed for the contemplated biological effect.

To satisfy the written description requirement, Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention (Applicants are directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112 ¶1 "Written Description" Requirement, Rev. 1, 2008; at http://www.uspto.gov/web/menu/written.pdf.). Moreover, MPEP 2163 states:[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Applicant's attention is also directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated: It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In view of the level of knowledge or skill in the art at the time of the invention, an Artisan of skill would not recognize from the disclosure that Applicant was in possession of the a transgenic fish line comprising chimeric construct comprising a fluorescent gene under control of any muscle specific promoter . The claimed invention as a whole is not adequately described if the claims require essential or critical elements or which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date for genus of muscle specific promoter that is capable of showing fluorescence upon exposure to any light including sunlight (see the reference of Gong et al supra). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of muscle specific promoter other then exemplified MLC2f containing SEQ ID no: 22 showing contemplated biological activity, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference

to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

The analysis above demonstrates that Applicant has not determined the core structure for full scope of the claimed genus for contemplated biological activity. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Thus, it is concluded that the written description requirement is not satisfied for the claimed genus.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a transgenic fish line comprising chimeric fluorescent gene under control of any muscle specific promoter showing contemplated biological activity (showing fluorescent upon exposure of transgenic fish to sunlight) at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Withdrawn-Double Patenting

Claims 1-3, 9-15, 20-21, 24, 30-32, 35-44 and 45 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 42-53, 58-60, 66-78 of copending Application No. 11/749,032. It is noted that applicant's have amended claims in '032 to limit the claims to ubiquitous promoter. Therefore, rejection is hereby withdrawn.

Maintained-Double Patenting

Claims 1-3, 9-16, 19-21, 24, 30-32, 35-42 remain rejected and newly added claims 43-45 are also rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U. S. Patent No. 7,135,613. Applicants argue that during the prosecution of USSN 09/913,898, Applicants attempted to introduce claims consistent with the claims pending in the present application (amendment dated May 9, 2003). In response to this attempted amendment, the Examiner refused entry of the amendment, taking the position that such claims were found not to be drawn to the invention elected in that case, which later became the '613 patent. In response, it is noted that Applicants attempts to introduce claims consistent with the claims pending in the present were refused by the examiner during the prosecution of USSN 09/913,898 because newly introduced claims were not directed to elected invention. It was indicated in the restriction requirement sent on 7/30/2003; 12/18/2003 that newly added business method claims are non responsive and not drawn to elected invention(MPEP 821.03).

In response, it is noted that Applicants' arguments would be persuasive, if the application were a divisional. However, instant application is a continuation application. **Applicant is required to change the relationship** continuation to divisional in order to overcome the rejection of record.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: In the instant case, even though the conflicting claims are not the same, they are not patentably distinct from each other because both sets of claims encompass a transgenic fish comprising a chimeric gene comprising a muscle specific promoter that drives the expression of a structural gene in said fish, wherein the transgenic fish contains said promoter in germ cells and/or in somatic cells and which is

capable of breeding with either a said transgenic fish or a non-transgenic fish to produce viable and fertile transgenic progeny. It is noted that structural gene is specifically exemplified as different fluorescent gene in US patent 7,135,613. Additionally, the only asserted use of the claimed composition in '613 is distribution of the transgenic ornamental fish to ornamental fish market. Therefore, instant claims differ only with respect to a broader scope distributing transgenic fish which encompass those specifically claimed in patent 7,135,613.

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Conclusion

No Claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Ellenberg, J., et al. (1998) BioTechniques 25: 838–846 teach variants of GFP with red- and blue-shifted fluorescence emissions that have been characterized, and possibly could be used for double labeling with two different-colored fusion proteins.

Bryan et al (US patent 5,876,995)

Higashijima et al (Dev Biol. 1997; 192(2): 289-99, IDS)

Abeywickrama et al (US Patent no: 5, 028,839, dated 7/2/1991)

Moss et al (Gene. 1996; 173: 89-98, IDS)

Chan et al (Abstract of paper presented at 1994 meeting on Zebrafish development and Genetics, abstract, IDS)

Yang et al (1998; 273(14):8212-6, IDS)

Living Colors Subcellular Localization Vectors (October 1998) CLONTECHniques XIII (4):8-9.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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